"DESIGN AND DEVELOPMENT OF MUCOADHESIVE BUCCAL PATCHES"

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1. INTRODUCTION

1. Introduction

Nowadays, requirement of design and development of novel dosage form is created to improve patient compliance, safety and efficacy. Buccal film is novel film technology which is fulfilled all these requirements. Buccal film is administered through buccal drug delivery system. Buccal film is small in size, dose, easily administered so that it is more palatable and acceptable dosage from than other buccal drug delivery system like wafers, lozenges, microparticles, gel, tablets. Buccal film is effective dosage form which improves bioavailability as it bypasses first pass metabolism. It is satisfactorily adhered to buccal layer of oral cavity so it is more convenient than other dosage form. It is cost effective, biodegradable, fast absorption, elegant, easy to handle, non irritating and no requirement of swallowing of drug henceforth it is more accepted dosage form by geriatric and pediatric patients.(Jagtap V, 2020).

1.1 Advantages of Buccal Film **(Jagtap V, 2020).**

- No risk of chocking.
- No need of chewing and swallowing.
- Rapid onset of action and minimum side effects.
- Accurate dosing compared to liquid dosage form.
- Taste masking is possible.
- Good mouth feel and good stability.
- Requires less excipient.
- Ease of transportation, storage and consumer handling.
- More Economical
- Ease of administration to pediatric, geriatric patients. Also to patients who are mentally retarded, disabled or non cooperative.
- Prolongs residence time of dosage form at site of absorption. So improves bioavailability.
- Drug can be protected from degradation in GI tract and acidic environment.

- Buccal film has large surface area that leads rapid disintegration and dissolution in oral cavity.

1.2 Disadvantages of Buccal Film **(Jagtap V, 2020).**

- Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. Instinctively swallowing of saliva results in a maximum part of dissolved or suspended released drug being removed from the site of absorption. Moreover, there is risk that the delivery system itself would be swallowed.
- Drug characteristics can make boundary for use of the oral cavity as a site for drug delivery. Taste, irritancy, allergy and adverse properties such as discoloration or erosion of the teeth can limit the drug candidate list for buccal route. Conventional type of buccal drug delivery systems did not allow the patient to concomitantly eat, drink or in some during talk.

1.3 Ideal Characteristics of Drug to be selected **(Jagtap V, 2020):-**

- No Bitter Taste
- Dose lower than 20mg.
- Low molecular weight
- Good stability in water and saliva.
- Ability to permeate oral mucosal tissue

1.4 Theories of Mucoadhesion **(Rajaram DM, 2017)**

There are five different theories, which explain phenomenon of mucoadhesion:

- **Electronic theory**

  This theory is based on fact that both mucus layer and biological materials have opposing electrical charges that able to create double electronic layer at the edge and thus helps in determination of *mucoadhesive* strength.

- **Wetting theory**

  Liquid or less viscous molecules enter into mucosal surface and fix themselves by counteracting the surface tension at the interface. This property relates to contact angle, wetting and spread ability capacity of molecule. (Figure 2) Contact angle (θ) and interfacial tension (γ) can be determined from following equation:

  $$\gamma SG = \gamma SL + \gamma LG\cos S = \gamma SG – (\gamma SL - \gamma LG)$$

  Where γLG is liquid–gas surface tension, γSL is solid–liquid surface tension and γSG is solid–gas surface tension.

- **Diffusion Theory**

  This theory suggests that *mucoadhesive* polymer diffuses into mucus layer by breaking glycoprotein chain network. This diffusion is time dependent and depends on diffusion coefficients and molecular weight of both phases.

- **Adsorption Theory**

  Weak Vander Waals forces and hydrogen bond mediated adhesion involved in adsoption theory is most accepted theory of mechanism of mucoadhesion. It involves primary and secondary bonding in exhibiting semi permanent surface interactions.

- **Fracture Theory**

  This is the second most accepted theory, which explains the forces required to detach the two surfaces following adhesion. This force is called as tensile stress or fracture strength and can be determined by following equation:

  Sm= Fm/Ao

  Where Sm: Tensile stress, Fm: maximum force of detachment

  andAo: surface area

  OR

  Sf= (gcE/c) ½

  Where Sf: fracture strength, gc: fracture energy (Wr + Wi = work done to produce new fracture surfaces + irreversible work of adhesion), E: Young's modulus of elasticity and c: critical crack length.

Each and every theory is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion.

1.5 Composition of buccal patches (Mishra S, 2012):-

A. Active ingredient.

B. Polymers (adhesive layer):-

Hydroxyethylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers.

C. Diluents:-

Lactose DC is selected as diluents for its high aqueous solubility, its flavouring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. other example : microcrystalline starch and starch.

D. Sweetening agents:-

Sucralose, aspartame, mannitol, etc.

E. Flavouring agents:-

Menthol, vanillin, clove oil, etc.

F. Backing layer:-

Ethyl cellulose, etc.

G. Penetration enhancer:-

Cyano acrylate, etc.

H. Plasticizers:-

PEG-100, 400, propylene glycol, etc

1.6 Evaluation of Buccal Patches (Kaur N, 2014)

The following tests are used to evaluate the Buccal Patches:

1. Weight uniformity: Five different randomly selected patches from each batch are weighed and the weight variation is calculated.

2. Thickness uniformity: The thickness of each patch is measured by using digital vernier callipers at five different positions of the patch and the average is calculated.

3. Folding Endurance: The folding endurance of each patch is determined by repeatedly folding the patch at the same place till it is broken or folded up to 300 times, which is considered satisfactory to reveal good film properties.

4. Surface pH: The prepared buccal patches are left to swell for 2 hrs on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature.51 The surface pH is determined by placing pH paper on the surface of the swollen patch. The mean of three readings is recorded.

5. Drug content uniformity: For drug content uniformity, a 3 cm patch (without backing membrane) is separately dissolved in 100 ml of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking. The resultant solution is filtered and the drug content of is estimated spectrophotometrically. The averages of three determinations are taken.

6. Swelling Index: Buccal patches are weighed individually (W1) and placed separately in petri dishes containing phosphate buffer pH 6.8. The patches are removed from the petri dishes and excess surface water is removed using filter paper. The patches are reweighed (W2) and swelling index (SI) is calculated as follows:

SI = (W2-W1)/W1

7. Moisture Content and moisture absorption : The buccal patches are weighed accurately and kept in dessicator containing anhydrous calcium chloride. After 3 days, the patches are taken out and weighed. The moisture content (%) is determined by calculating moisture loss (%) using the formula:

Moisture content (%) = Initial weight - Final weightx100/Final weight

The buccal patches are weighed accurately and placed in a dessicator containing 100 ml of saturated solution of aluminium chloride, which maintains 76% and 86% humidity (RH). After 3 days, films are taken out and weighed. The moisture absorption is calculated using the formula: Moisture absorption (%) = Final weight-Initial weightx100 Initial weight

8. *In-vitro* drug release: The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and

replaced with fresh medium. The samples are then filtered through wattman filter paper and analyzed for drug content after appropriate dilution.

9. *Ex-vivo* mucoadhesion time: The *ex-vivo* mucoadhesion (residence) time is determined by locally modified USP disintegration apparatus using 800 mL of simulated saliva (pH 6.2) and the temperature is maintained at (37±1) °C. A porcine buccal mucosa obtained from local slaughter house within 2 h of slaughter is used to mimic the human buccal mucosa in the *in-vivo* conditions. The mucosal membrane is carefully separated by removing the underlying connective tissues using surgical scissors. The separated mucosal membrane is washed with deionized water and then with simulated saliva (pH 6.2). Porcine buccal mucosa (3 cm diameter) is glued on the surface of a glass slab. One side of the buccal patch is hydrated with one drop of simulated saliva (pH 6.2) and brought into contact with porcine buccal mucosa by gentle pressing with a fingertip for few seconds. The glass slab is vertically fixed to the shaft of the disintegration apparatus and allowed to move up and down (25 cycles per min). The patch is completely immersed in simulated saliva at the lowest point and is out of the solution at the highest point. The time of complete erosion or detachment of the patch from the mucosal surface is recorded as *ex-vivo* mucoadhesion time.

10. *Ex-vivo* mucoadhesive strength: The force required to detach the attachment of mucoadhesive film from the mucosal surface was applied as a measure of the mucoadhesive strength. This study was carried out on a specially fabricated physical balance assembly. Porcine buccal mucosa was glued on a dry petri dish surface by placing the mucosal surface outward and it was moistened with few drops of simulated saliva (pH 6.2). The right side pan of the balance was replaced by a glass disc glued with a buccal patch of 3 cm diameter. The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. A weight of 5 g (w1) was removed from the left pan, which lowered the pan and buccal patch was brought in contact with pre moistened mucosa for 5 min. Then weights were increased gently on the left pan until the attachment breaks (w2). The difference in weight (w2-w1) was taken as mucoadhesive strength. The mucoadhesive force was calculated from the following equation:

Mucoadhesive force (kg/m/s) =

Mucoadhesive strength (g) x acceleration due to gravity 1000

Here, acceleration due to gravity 9.8 m/s−1

11. *Ex-vivo* permeation study: The *ex-vivo* buccal permeation through the porcine buccal mucosa is performed using a modified Franz glass diffusion cell. Porcine buccal mucosa is obtained from a local slaughterhouse and used within 2 h of slaughter. Freshly obtained porcine buccal mucosa is mounted between the donor and receptor compartments. The patch is placed on the smooth surface of mucosa by gentle pressing and the compartments are clamped together. The donor compartment is moistened with 1 ml of simulated saliva (pH 6.2) and the receptor compartment is filled to touch the membrane with a mixture of 100 ml of ethanol and isotonic phosphate buffer (20:80). The fluid motion in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. The temperature is maintained at (37±0.2) °C by water jacket surrounding the chamber. At predetermined time intervals, a 2 ml sample is withdrawn (replaced with fresh medium) and analyzed spectrophotometrically. The permeation study is performed in triplicate.

12. Stability Studies in Human Saliva:

The stability study of buccal patches is performed in natural human saliva. The human saliva is collected from humans (age 18-50 years). Buccal patches are placed in separate Petri dishes containing 5 ml of human saliva and placed in a temperature-controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), the patches are examined for change in colour, shape and drug content.

2. LITERATURE REVIEW

2.1 Jeganath S *et al* (2019) was studied the chlorzoxazone mucoadhesive buccal patches, to increase therapeutic efficacy, better bioavailability, and reduce the side effect, and to provide controlled release of drug and improve patient compliance. Buccal films of chlorzoxazone was prepared by solvent casting technique using film‐forming mucoadhesive polymers such as hydroxypropyl methylcellulose and ethyl cellulose with different concentrations. Five different formulations were prepared and evaluated with respect to patch thickness, surface pH, folding endurance, drug content uniformity, swelling index, determination of moisture and moisture absorption, and in vitro release study. Compatibility study was carried out by Fourier transform infrared (FT-IR) spectral analysis.

2.2 Dubey A *et al* (2018) was studied Buccal patch is a non-dissolving thin matrix modified release dosage form which was developed to administer into the unconscious and less co-operative patients. The mucoadhesive buccal patches of hydrochlorothiazide (HCZ) and atenolol (ATN) was prepared by solvent casting technique using various concentrations of sodium alginate, hydroxyl propyl methyl cellulose, carbopol 934P and sodium carboxy methyl cellulose polymer and polyvinyl alcohol as a backing layer. The formulated patches was evaluated for their physicochemical parameters like thickness, weight variation, surface pH, content uniformity, folding endurance, swelling percentage studies and tensile strength, in vitro and ex vivo drug permeation.

2.3 Laisa L *et al* (2018) was studied to evaluate, by means of a systematic review with meta-analysis, the data related to the final quality of this technology. The development of oral tablets with 100 to 150 mg, including soluble drugs and sustained release for 6 hours or more, is a consensus. The most frequent polymers used are those derived from cellulose, Carbopol (CBM), Chitosan (CS), and Gums, alone or blended, with adhesive strength in the order.

2.4 Mishra S *et al* (2012) was studied mucoadhesive buccal tablets of Simvastatin using

mucoadhesive polymers. Simvastatin has short biological half-life (3hr), high first-pass metabolism and poor oral bioavailability (5%), hence an ideal candidate for buccal delivery system. From the present study carried out on simvastatin buccal patches prepared from 1% eudragit-RS100 and variable amount of different polymer composite, PVP, PVA, HPMC and EC. The buccal patches prepared using 50% glycerine w/w of polymer weight was found to have good physical characteristics.

2.5 Saraf SA *et al* (2011) was studied the buccal patch for systemic administration of acyclovir in the oral cavity was developed using polymers hydroxy propyl methyl cellulose (K4M), hydroxy propyl methyl cellulose (K15M), sodium carboxy methyl cellulose and poly vinyl pyrolidone (K30), plasticizer poly ethylene glycol (400) and a backing membrane of Eudragit (RL100). The films were evaluated in terms of swelling, residence time, mucoadhesion, release, and organoleptic properties.

2.6 Puratchikody A *et al* (2011) was studied the Salbutamol sulfate patches were prepared using Eudragit L-100, HPMC, PVA and Carbopol 934 in various proportions and combinations using PEG-400/PG as plasticizers. Patches were laminated on one side with a water impermeable backing layer for unidirectional drug release.

3. AIM AND OBJECTIVE

3.1 Aim

To design and develop of Mucoadhesive Buccal Patches.

3.2 Objective

1. To provide prolonged and constant therapeutic effect.
2. To reduce the dosing frequency and therefore improve the patient compliance
3. To mask the taste and odor.
4. To provide controlled, sustained and targeted delivery of the drug.

4. PLAN OF WORK

4.1. Literature survey

4.2. Procurement of Drugs and Excipients

4.3. Preformulation study

4.4. Formulation of Buccal Patches by solvent casting technique.

4.6. Evaluation of Buccal Patches

a. Weight uniformity

b) Thickness uniformity

c) Folding Endurance

d) Surface pH

e) Drug content uniformity

f) Swelling Index

g) Moisture Content and moisture absorption

h) *In-vitro* drug release

i) *Ex-vivo* mucoadhesion time

j) *Ex-vivo* mucoadhesive strength

k) *Ex-vivo* permeation study

l) Stability Studies

4.7 Results and Discussion

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